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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

18N2/0711

ART UNIT	PAPER NUMBER
1819	11

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DATE MAILED: 07/11/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/25/97 & 7/3/97

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 37-55 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☑ Claim(s) 37, 38, 40-45 & 52 is/are allowed.
☑ Claim(s) 39, 46-51, & 53-55 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-496/40517

The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1819.

Claims 1-36 are cancelled, claims 37-39 are amended, and new claims 40-50 have been added, as requested in the amendment filed 3/25/97. Claims 37-40 and 46-50 have been amended and new claims 51-55 have been added as requested in the supplemental amendment filed 7/3/97. Claims 37-55 are now pending in the application and have been examined.

The objection to the specification and rejection of claims under 35 U.S.C. § 112, first paragraph, as failing to provide adequate written description of the invention and to adequately teach how to make and use the claimed invention, have been partially withdrawn in view of the amendments and Applicants' arguments filed 3/25/97 and 7/3/97. The remaining grounds for objecting to the specification and rejecting claims under 35 U.S.C. § 112, first paragraph, are stated below.

Claims 39 and 48-50 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is only enabling for the claimed invention wherein the recited packaging cell line is a 293-derived cell line. At the time the application was filed, it was recognized that, due in part to the general cytotoxicity of expression of adenovirus E1 early region genes in eukaryotic cells, the cell lines which were available to one skilled in the art for producing useful amounts of recombinant E1-deleted adenovirus were 293-derived cell lines (see Fallaux et al., pp. 215, 221). At the time the application was filed, it was unclear why 293 cells are special in this regard, and it was not known how to successfully obtain non-293-derived cells which would serve as hosts for successful production of recombinant E1-deleted adenovirus. In the absence of evidence to the contrary,

one skilled in the art would reasonably have considered that undue experimentation would have been required to make the claimed invention except wherein the recited packaging cell line which is a 293-derived cell line.

Claims 46, 48, 49, 53, and 54 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is enabling for the claimed invention wherein the recited recombinant adenoviral vector is deficient in E1 and E4 early gene regions, but has a functional E2A early gene region, and wherein the recited packaging cell line is a 293-derived cell line that is stably transformed with an expression construct comprising an inducible promoter linked to adenoviral E4 early region genes, for rescue of recombinant adenovirus lacking functional E1 and E4 early gene regions, but is not also transformed with an expression construct directing expression of E2A early region genes. The specification does not enable making and using the recited packaging cell line which supports replication of a recombinant adenovirus deficient in E1, E4 as well as E2A early gene regions. It is well known that expression of E2A early region genes is toxic to the host cell (see Klessig et al., 1984). Applicants have demonstrated the unexpected result that 293 cells can survive while expressing E1 early region genes along with the low level of expression of E4 early region genes allowed by the uninduced MIP (α) promoter. Applicants have provided no data regarding whether 293 cells can survive while expressing E1 and E4 early region genes along with the cytotoxic E2A genes. Given the recognition that expression of any of the E1, E4 and E2A gene regions in a eukaryotic cell is generally cytotoxic, one skilled in the art at the time the application was filed would have considered it unpredictable and doubtful whether a transformed host cell would survive and grow after being transformed to express all three of said E1, E4 and E2A gene regions. The

specification provides no examples demonstrating that such a cell would survive and function as a host for replication of the recombinant adenovirus. In the absence of evidence showing that such a host cell transformed to express said E1, E4 and E2A gene regions would survive and grow, one skilled in the art would reasonably have considered that undue experimentation would have been required to make the claimed invention except wherein the recited packaging cell line is a 293-derived cell line that is stably transformed with an expression construct comprising an inducible promoter linked to adenoviral E4 early region genes, for rescue of recombinant adenovirus lacking functional E1 and E4 early gene regions and comprising an operable E2A gene region.

Claims 39, 48-50, and 55 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is enabling for the claimed packaging cell line wherein the nucleic acid sequence in said cell line which supplies the function of the E4 early region is operably linked to an inducible promoter. The specification and prior art (e.g. Gregory et al., p. 55) clearly teach that expression of E4 region genes essential for adeniviral replication in cells is cytotoxic to the host cells. The only packaging cell lines disclosed in the specification comprising nucleic acid sequences which complement the E4 region which survive and grow are cells have an inducible promoter operably linked to said nucleic acid sequences, and one skilled in the art at the time the application was filed would reasonably have considered that undue experimentation would have been required to make the claimed invention except wherein the recited packaging cell line is one wherein the nucleic acid sequence in said cell line which supplies the function of the E4 early region is operably linked to an inducible promoter.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

Claims 51 and 53 are drawn to a recombinant adenovirus requiring complementation of E1 and E4 region genes in which the only region of the E4 region which is deleted or mutated in open reading frame 4 (orf 4). Gregory et al. (WO 94/12649) teach that recombinant adenovirus in which all of the E4 region except orf 6 has been deleted is able to replicate in 293 cells (p. 59). Ketner et al. (Nucleic Acids Research, 1989) also teach that a plasmid encoding orf 6 is sufficient to complement recombinant adenovirus with an E4 deletion. Given the teaching by Gregory et al. and Ketner et al. that a recombinant adenovirus replicates successfully in 293 cells when orf 4 is the only region of the E4 region which is deleted or mutated, and given the lack of guidance in the specification regarding the conditions or steps employed to prevent replication of recombinant adenovirus wherein orf 4 is the only region of the E4 region which is deleted or mutated, undue experimentation would have been required by one skilled in the art at the time the application was filed to make and use the claimed invention.

Claims 51 and 53 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 46-50 and 53-55 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 46-50 is indefinite because the use of the term "optionally" in said claims makes it unclear precisely what is the claimed invention.

Claim 46 because is also indefinite because it is unclear whether or not the recited optional deletion adenoviral vector is the same molecule as the first-recited vector comprising the multiple deletions.

The rejections of claims under 35 U.S.C. § 102(a) as anticipated by Engelhardt et al. and by Armentano et al. have been withdrawn in view of the amendments filed 3/25/97 and 7/3/97.

The rejections of claims under 35 U.S.C. § 102(b) as anticipated by Klessig et al. and by Graham et al. have been withdrawn in view of the amendments filed 3/25/97 and 7/3/97.

The rejections of claims under 35 U.S.C. § 103 over Weinberg et al., in view of additional references, has been withdrawn in view of the amendments filed 3/25/97 and 7/3/97.

Claims 40-45 are allowable over the prior art of record, because at the time the application was filed, it was unpredictable whether or not a cell line transformed by a plasmid comprising an inducible promoter operably linked to E4 adenoviral early gene region nucleic acid sequences encoding a cytotoxic gene product would survive and grow, so that it was unclear whether or not the recited plasmid would be useful. Claim 45 is also allowable over the prior art of record because at the time the application was filed, there was no suggestion in the prior art to make a plasmid having the same nucleotide sequence of the recited plasmid.

Claims 37-39 and 46-55 are allowable over the prior art of

record, because at the time the application was filed, it was unpredictable whether or not a cell line transformed to contain functional genes encoding both the E1 and E4 adenoviral early region genes would survive and grow. Applicants' successful demonstration that 293 cells stably transformed with an expression construct comprising an inducible promoter linked to the adenoviral E4 early region genes would survive, grow, and efficiently produce recombinant adenovirus with deletions in both E1 and E4 regions was an unexpected and unobvious result.

Claims 37, 38, 40-45, and 52 are allowable.

Applicant's arguments filed 3/25/97 have been fully considered but they are not deemed to be persuasive.

Applicants urge that objection to the specification and rejection of the claims under 35 U.S.C. § 112, first paragraph, for failure to adequately teach how to use the invention, be reconsidered and withdrawn, because the invention recited in the amended claims is fully enabled by the specification.

The examiner maintains that the remaining grounds for rejection of the claims under 35 U.S.C. 112, first paragraph, are based on reference to relevant teachings in the published literature, and on consideration of the nature of the invention, the quantity of experimentation required, the amount of guidance presented in the specification, the presence and absence of working examples, the state of the prior art, the degree of predictability of successful operation of the claimed invention, and the breadth of the claims, as called for in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988), as discussed in the previous office action. Therefore, those portions of the objection to the specification and rejection of the claims under 35 U.S.C. § 112, first paragraph, in the previous office action and are maintained as discussed above are proper.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

General Information Regarding Further Correspondence

Any inquiry concerning this or earlier communications from the examiner should be directed to Dr. Charles Rories, Group 1800, Art Unit 1819, at telephone number (703)-308-1120. The examiner can normally be reached from 7:30 AM to 5:00 PM on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at (703)-308-2035.

Papers related to this application may be submitted to Art Unit 1819 in Crystal Mall I by facsimile transmission to telephone number (703)-308-0294. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Any inquiry of a general nature or relating to the status of this application, should be directed to the Group 1800 receptionist, at telephone number (703)-308-0196.

7 July 1997

Charles C. P. Rories
Patent Examiner
Art Unit 1819